

Propranolol or Hydrochlorothiazide Alone for the Initial Treatment of Hypertension

IV. Effect on Plasma Glucose and Glucose Tolerance

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SUMMARY To evaluate the short-term and long-term effectiveness of propranolol and hydrochlorothiazide monotherapy for hypertension, 683 hypertensive men were randomized to treatment with either propranolol or hydrochlorothiazide. Both drugs increased the average fasting plasma glucose level by approximately 5 mg/dl after 10 weeks ($p < 0.001$) and 1 year ($p < 0.001$) of treatment, but the elevation persisted only in the propranolol-treated group 1 month after discontinuing the year-long treatment ($p < 0.01$). A subset of 191 patients had 2-hour glucose tolerance tests. Hydrochlorothiazide increased the average 2-hour oral glucose tolerance test result by 18.0 mg/dl after 10 weeks ($p < 0.001$), an increase significantly higher than that induced by propranolol ($p < 0.012$). After 1 year of treatment, however, propranolol also increased the average 2-hour oral glucose tolerance test result ($p < 0.05$) and there was no significant difference between drugs. The hyperglycemic effects were dose-related, which suggests that both drugs should be administered at their lowest effective dosage. The clinical importance of the persistent fasting plasma glucose elevation in propranolol-treated patients 1 month after discontinuing treatment is unknown. (Hypertension 7: 1008-1016, 1985)

KEY WORDS • hyperglycemia • side effects • hypertensive therapy

It has been known for well over 20 years that thiazide diuretics elevate blood glucose levels and impair glucose tolerance in a substantial proportion of patients treated with therapeutic doses for hypertension.^{1,2} These effects have been noted during both short-term and long-term treatment^{3,4} and represent a complicating factor in managing hypertensive patients with borderline or frank diabetes.⁵ In addition, on the suspicion that the vascular lesions of diabetes might be related to the blood glucose level,⁶⁻⁸ it has been suggested that treatment with thiazide diuretics could enhance the vasculopathic potential of hypertension by increasing blood glucose levels.⁴

β -Blockers have been suggested as an alternative to thiazides at the first level of the stepped-care scheme. With respect to this consideration, the development of diabetes has been mentioned as one of the specific disadvantages of thiazides as compared to β -blockers.⁹

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The main purpose of the present study was to evaluate the short-term and long-term effectiveness of propranolol (PROP) as compared to hydrochlorothiazide (HCTZ) in the monotherapy of hypertension. Herein, we report on that aspect of the study that compares the effects of both drugs on fasting plasma glucose levels and glucose tolerance.

Materials and Methods

The design of this study has been described previously.^{10, 11} Briefly, this was a seven-hospital, cooperative, double-blind, randomized clinical trial. Hypertensive men, aged 21 to 65 years, were admitted to the trial after appropriate informed consent if their sitting diastolic blood pressure (DBP) was in the range of 95 to 114 mm Hg after a minimum of 2 weeks without antihypertensive therapy. Subjects were excluded if they had a severe complication of hypertension, secondary hypertension, a serious systemic disease, or a contraindication to treatment with PROP or HCTZ. Patients with diabetes mellitus were excluded if the diabetes was unstable, was of preadult onset, or required treatment with insulin. No selection was attempted or made on the basis of family or personal history of diabetes, dietary intake, or other treatment for diabetes.

There was a prerandomization, single-blind placebo period of 4 weeks to obtain baseline data and to determine eligibility, defined as an average DBP in the range of 95 to 114 mm Hg on two consecutive visits and pill counts of the placebo within a designated acceptable range. Eligible patients were randomly assigned in a double-blind fashion to receive either PROP or HCTZ to start the titration dose finding period (phase A). At a maximum of seven clinic visits 1 or 2 weeks apart during a 10-week period, daily doses were titrated from 80 mg to 160, 240, 320, 480, or 640 mg for PROP and from 50 mg to 100 or 200 mg for HCTZ. Both drugs were given in equal, twice-daily divided doses. The titration was continued until either a DBP below 90 mm Hg was achieved or there were side effects. No specific dietary restrictions were prescribed. To enter the long-term treatment period (phase B) of the study, the patient had to achieve either a DBP below 90 mm Hg on two consecutive phase A visits or an average DBP during the last two consecutive visits of phase A below 100 mm Hg and at least 6 mm Hg below the baseline average. The long-term treatment phase (phase B) consisted of 12 visits at 4-week intervals for a total of 48 weeks of continuous treatment.

Additional adjustments to dosage were permitted during the long-term treatment phase according to DBP, compliance, and side effects. Subjects could be terminated for severe side effects or for lack of designated antihypertensive effectiveness within specified periods. After the long-term treatment phase, there were two weekly visits for dose tapering and two further weekly visits for the final placebo period.

Laboratory studies including the standard urinalysis, complete blood count, and blood chemistry tests using automated analyzers were done just before beginning the dosage titration phase, after its completion (phase A), at the end of the long-term treatment phase (phase B), and at the end of the 2-week final placebo phase. Two of the seven participating hospitals (Allen Park, MI; San Juan, Puerto Rico) volunteered to perform 2-hour oral glucose tolerance tests (2-hour OGTT) at randomization, at the end of phase A, and at the end of phase B. Throughout the study, the laboratories at all the participating hospitals satisfied the quality control requirements of the American College of Pathologists.

The patients who had a 2-hour OGTT received a 300-g carbohydrate diet for 3 days before the test and were instructed to take only water after 1900 hours on the night before the test. The next morning, a fasting blood sample was drawn and, if it was less than 150 mg/dl, the subject was given 7 fl oz of Glucola containing 75 g of glucose. A repeat plasma glucose sample was drawn 2 hours later. True glucose values were determined using the glucose oxidase method.

This study was designed by a committee that included biostatisticians, some of whom participated in the analysis of the data and in the monitoring of the study. Paired and unpaired Student's *t* tests, Pearson *r* correlations, chi-square tests, and analyses of covariance

were used to assess statistically significant differences (defined as $p < 0.05$) between groups of data.

Results

Of the 906 subjects entering the study, 683 (75.4%) were randomized; 340 to PROP and 343 to HCTZ. The most common causes for prerandomization dropout were noncompliance and blood pressure above or below the randomization criteria. Only four subjects were taking oral hypoglycemic agents at randomization; one was assigned to PROP and three to HCTZ. Blacks constituted 57.6% of the patients randomized to PROP and 56.0% of those randomized to HCTZ; the difference was not significant. Some clinics had a higher percentage of blacks than others, but the racial composition between the drug groups was not significantly different within any of the clinics.

Phase A was completed by 610 subjects; 298 received PROP and 312 received HCTZ. More subjects receiving HCTZ (128) than PROP (102) completed phase A before the full 10 weeks was over, because they achieved earlier a DBP less than 90 mm Hg on two consecutive visits; therefore, the average duration of phase A was shorter for HCTZ-treated than for PROP-treated subjects. Of the 610 subjects who completed phase A, only 491 entered the study early enough to be eligible for long-range treatment. Of this number, 394 met the criteria for entering the long-term treatment period (phase B) of the study; 182 received PROP and 212 received HCTZ. Phase B was completed by 125 subjects receiving PROP and by 177 receiving HCTZ.

The baseline characteristics of all randomized patients are shown in Table 1; there were no significant differences between the two groups. The baseline variables were also studied for the subgroups of subjects that completed phase A and phase B. There were no significant differences between these subgroups either, except for a lower baseline serum calcium level in the PROP-treated subgroup that completed phase B ($p = 0.037$).

Reasons for terminations were classified as either administrative (e.g., failure to return to clinic, stopping treatment) or medical (e.g., inadequate DBP control, side effects). The administrative terminations were equally divided between both groups, but the medical terminations, particularly inadequate DBP control, were more frequent in the PROP-treated group. The total number of terminations in the PROP-treated subjects compared with the HCTZ-treated subjects were 42 to 31 during phase A and 57 to 35 during phase B. This aspect of the study has been described in previous communications.^{10, 11}

No subject was terminated for a diabetes-related reason. Only one subject was started on a regimen of oral hypoglycemic agents de novo during the study. As the study progressed, the total number of subjects receiving oral hypoglycemic agents was very small: one at the end of phase A, two at phase B, and one at the final placebo phase. All had been randomized to HCTZ.

TABLE 1. Comparison of Baseline Characteristics of the Patient Populations Randomized to Propranolol and Hydrochlorothiazide at All Hospitals

Variable	Propranolol		Hydrochlorothiazide	
	No. of subjects	Mean \pm SD	No. of subjects	Mean \pm SD
Age (yr)	340	49.6 \pm 9.8	343	49.8 \pm 9.9
Black (%)	340	57.6	343	56.0
Weight (lb)	340	191.5 \pm 33.4	343	189.4 \pm 30.9
Diastolic blood pressure (mm Hg)	340	101.6 \pm 4.6	343	101.3 \pm 4.5
Systolic blood pressure (mm Hg)	340	146.0 \pm 14.4	343	146.5 \pm 15.8
Creatinine (mg/dl)	339	1.18 \pm 0.20	339	1.16 \pm 0.21
Potassium (mEq/L)	339	4.2 \pm 0.39	342	4.3 \pm 0.68
Uric acid (mg/dl)	335	6.4 \pm 1.31	342	6.5 \pm 1.45
Cholesterol (mg/dl)	335	221.1 \pm 47.4	336	224.3 \pm 47.0
Triglycerides (mg/dl)	336	165.8 \pm 140.6	338	184.1 \pm 197.8
Calcium (mg/dl)	257	9.5 \pm 0.50	259	9.4 \pm 0.90
Fasting plasma glucose (mg/dl)	337	100.0 \pm 22.7	343	100.4 \pm 25.2

There were no significant differences between groups.

The average dose of medication found necessary to control blood pressure in each group at the end of phase A was 268 mg/day for PROP and 93 mg/day for HCTZ. During phase B, dosage increases to maintain blood pressure control were necessary in 37.6% of PROP-treated and in 20.9% of HCTZ-treated patients; dosage decreases were necessary in 0.8% of PROP-treated and in 4% of HCTZ-treated patients.

At the two participating hospitals that performed the 2-hour OGTT, 96 subjects were randomized to PROP and 95 to HCTZ. Whites outnumbered blacks 53 to 43 in the group randomized to PROP and 56 to 39 in the group randomized to HCTZ. Eight-eight subjects receiving PROP and 89 receiving HCTZ completed phase A, and 38 subjects receiving PROP and 49 receiving HCTZ completed phase B.

The baseline characteristics were studied at the two hospitals for the randomized groups and for the sub-

groups that completed phase A and phase B. There were no significant differences between them. However, there were several statistically significant differences in the baseline characteristics between the subjects at the two hospitals (Table 2). The subjects at Allen Park were significantly younger and heavier and had significantly higher average serum cholesterol and serum calcium levels than those at San Juan. On the other hand, the San Juan subjects had significantly higher systolic blood pressure and DBP, serum triglyceride levels, fasting plasma glucose (FPG) levels, and 2-hour OGTT results.

Fasting Plasma Glucose Levels

Table 3 shows the average FPG level at all the hospitals for all phases and the differences between each phase and the baseline value of the same group of patients. For all subjects, the FPG level increased sig-

TABLE 2. Significant* Baseline Characteristic Differences at the Two Hospitals that Performed 2-Hour Oral Glucose Tolerance Tests

Variable	Allen Park, Michigan		San Juan, Puerto Rico		p
	No. of subjects	Mean \pm SD	No. of subjects	Mean \pm SD	
Age (yr)	91	49.0 \pm 10.2	100	52.3 \pm 7.7	0.014
Black (%)		73.6		15.0	
Weight (lb)	91	190.1 \pm 30.7	100	178.0 \pm 25.8	0.003
Diastolic blood pressure (mm Hg)	91	102.4 \pm 5.2	100	103.8 \pm 3.6	0.047
Systolic blood pressure (mm Hg)	91	139.6 \pm 12.0	100	149.1 \pm 11.5	0.000
Cholesterol (mg/dl)	91	216.7 \pm 39.7	97	203.8 \pm 48.4	0.048
Triglycerides (mg/dl)	91	157.5 \pm 123.5	100	240.6 \pm 192.5	0.000
Calcium (mg/dl)	91	9.6 \pm 0.5	100	9.4 \pm 0.5	0.029
Fasting plasma glucose (mg/dl)	90	93.7 \pm 17.5	100	107.8 \pm 27.4	0.000
2-hour OGTT (mg/dl)	88	105.3 \pm 39.0	95	141.5 \pm 65.1	0.000

OGTT = oral glucose tolerance test.

*p < 0.05.

TABLE 3. Average Fasting Plasma Glucose Values at All Hospitals for the Various Phases

Variable	All patients		Propranolol		HCTZ		<i>p</i> (between drugs)
	No. of subjects	Mean \pm SD	No. of subjects	Mean \pm SD	No. of subjects	Mean \pm SD	
Phase A	534	104.0 \pm 21.8	259	102.3 \pm 20.2	275	105.6 \pm 23.1	NS
Δ baseline	532	4.0 \pm 20.3*	257	4.0 \pm 17.1*	275	4.0 \pm 22.9†	NS
Phase B	294	106.2 \pm 26.6	120	105.9 \pm 21.8	174	106.4 \pm 29.5	NS
Δ baseline	293	5.4 \pm 25.1*	119	6.4 \pm 18.4*	174	4.7 \pm 28.9‡	NS
Δ from phase A	256	1.6 \pm 20.0	103	3.1 \pm 17.9	153	0.6 \pm 21.4	NS
Final placebo	265	102.3 \pm 23.2	110	105.9 \pm 22.9	155	99.7 \pm 23.2	0.032
Δ baseline	264	0.7 \pm 23.7	109	4.6 \pm 18.3†	155	-2.0 \pm 26.5	<0.017

Change represents the difference between a phase and the respective group baseline average.

HCTZ = hydrochlorothiazide; NS = not significant ($p > 0.05$).

* $p < 0.001$, † $p < 0.01$, ‡ $p < 0.05$, within groups.

nificantly from the respective group baseline, in both phase A and phase B ($p < 0.001$). Each drug group by itself also showed significant FPG level increases from its baseline in both phases. The average increases in FPG level were relatively small: 4.0 mg/dl for each drug in phase A, and 4.7 mg/dl for PROP and 6.4 mg/dl for HCTZ in phase B. When the drug groups were compared with each other, neither the average values in each phase nor the changes between phases were significantly different. However, compared with their respective group baseline, the FPG level remained significantly elevated in the 109 PROP-treated subjects who completed the final placebo period, whereas the FPG level in the HCTZ-treated group returned to its baseline. The difference was also significant between drugs, between both the levels ($p = 0.032$) and the changes from baseline ($p < 0.017$).

The number of subjects who crossed diabetes diagnostic limits was studied according to accepted standards that define the FPG level as definitely normal below 115 mg/dl and definitely abnormal above 139 mg/dl.¹² The percentage change within each of these categories in those subjects who completed each phase is shown in Figure 1. Of 119 subjects taking PROP who completed phase B, there were 12% fewer with a definitely normal FPG level than at baseline ($p = 0.016$). There were no other statistically significant changes in the percentages.

Two-Hour Glucose Tolerance Test

Table 4 shows the average 2-hour OGTT results for the two hospitals at randomization and at each phase. The differences between each phase and the baseline average of the respective group of subjects are also shown. For all subjects, there were significant average increases from baseline to phase A ($p = 0.008$), from baseline to phase B ($p = 0.002$), and from phase A to phase B ($p = 0.003$). Values in HCTZ-treated subjects increased significantly from baseline both to phase A ($p = 0.001$) and to phase B ($p = 0.024$), while values in PROP-treated subjects increased significantly only from baseline to phase B ($p = 0.014$). Analyses of between-drug differences indicated that the HCTZ-treated subjects exhibited a significantly higher level

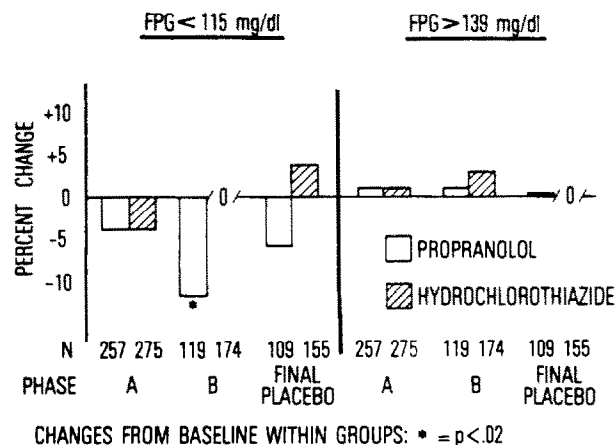


FIGURE 1. Changes in the prevalence of fasting plasma glucose (FPG) levels less than 115 mg/dl and more than 139 mg/dl in those subjects completing phase A, phase B, and final placebo phase. N = number of subjects in each group. Data are from all seven hospitals.

($p = 0.007$) and a greater change from baseline ($p = 0.012$) than the PROP-treated subjects during phase A. There were no significant differences between drugs during phase B.

The number of patients who crossed diabetes diagnostic limits was studied according to accepted standards that define the 2-hour OGTT as definitely normal below 140 mg/dl and definitely abnormal above 199 mg/dl.¹² The percentage change in each of these categories in those subjects who completed each phase is shown in Figure 2. In 80 HCTZ-treated subjects completing phase A, there were 21% fewer with a definitely normal ($p = 0.0001$), and 11% more with a definitely abnormal ($p = 0.027$), 2-hour OGTT result than at baseline. Both differences were also significant between drugs ($p = 0.0002$ and $p = 0.039$ respectively). During phase B the only significant difference was in the 45 HCTZ-treated subjects: 22% fewer subjects had a definitely normal 2-hour OGTT result than at baseline ($p = 0.016$). However, this difference was not significant between drugs.

TABLE 4. Average 2-Hour Oral Glucose Tolerance Test Values at Randomization and the Various Phases, Combined for the Two Hospitals

Variable	All patients		Propranolol		HCTZ		p (between drugs)
	No. of subjects	Mean \pm SD	No. of subjects	Mean \pm SD	No. of subjects	Mean \pm SD	
Randomization	209	123.0 \pm 55.6	90	119.5 \pm 48.3	93	128.5 \pm 64.3	NS
Phase A	156	131.4 \pm 58.5	75	118.5 \pm 45.4	81	143.2 \pm 66.6	0.008
Δ baseline	154	9.5 \pm 43.7*	74	0.4 \pm 36.2	80	18.0 \pm 48.4†	0.012
Phase B	80	155.8 \pm 90.9	35	147.7 \pm 79.2	45	162.1 \pm 99.4	NS
Δ baseline	79	22.5 \pm 61.9*	34	18.1 \pm 40.8‡	45	25.9 \pm 74.3‡	NS
Δ from phase A	75	13.7 \pm 54.8*	32	18.4 \pm 59.9	43	10.8 \pm 51.3	NS

Change represents the difference between a phase and the respective group baseline average.

HCTZ = hydrochlorothiazide; NS = not significant ($p > 0.05$).

* $p < 0.01$, † $p < 0.001$, ‡ $p < 0.05$, within groups.

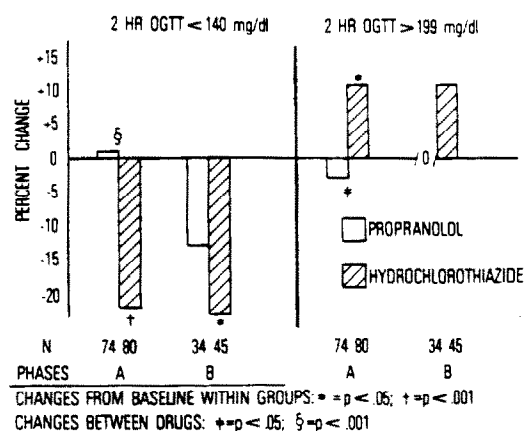


FIGURE 2. Changes in prevalence of 2-hour oral glucose tolerance test (OGTT) results less than 140 mg/dl of glucose and more than 199 mg/dl of glucose in those patients completing phases A and B. N = number of subjects in each group. Data are from two hospitals (Allen Park, MI and San Juan, PR).

Relationship with Drug Dosage

Figure 3 shows the average changes in plasma glucose level from the respective group baseline through phases A and B according to dosage. Subjects that were taking more than 320 mg/day of PROP had a significantly greater increase from baseline in FPG level ($p < 0.001$) and in 2-hour OGTT results ($p < 0.05$) during phase B than did those who were taking a lower dosage. There were no significant differences between these dosage subgroups from baseline to phase A.

Subjects taking 100 or 200 mg of HCTZ per day had a significantly greater increase in FPG level from baseline during both phase A ($p < 0.001$) and phase B ($p < 0.05$) than did those who were taking 50 mg of HCTZ per day. The 2-hour OGTT result increases were greater in the higher dosage subgroup during both phases, but the differences were not significant. However, there were only seven subjects in the low dosage subgroup at phase B.

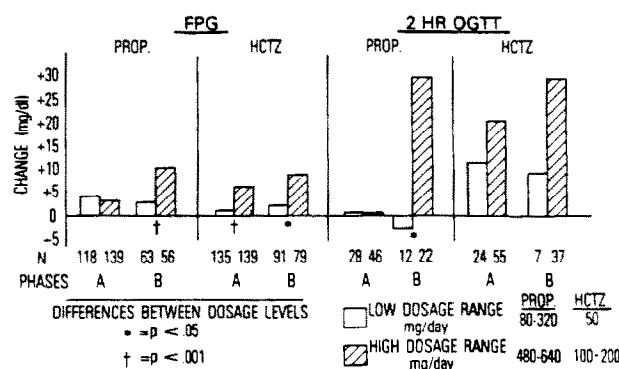


FIGURE 3. Changes in fasting plasma glucose (FPG) levels and 2-hour oral glucose tolerance test (OGTT) results in those subjects completing phase A and phase B grouped by low and high dosage of propranolol (PROP) and hydrochlorothiazide (HCTZ). N = number of subjects in each group. The FPG data are from all hospitals; 2-hr OGTT data are from two hospitals (Allen Park, MI and San Juan, PR).

Other Analyses

Analyses of covariance were performed to test the significance of the differences between the drugs in terms of plasma glucose level after adjustment for the effect of interhospital differences, serum triglyceride levels, body weight, and race. The results for values at the various phases and the interphase changes are shown in Table 5.

The differences remained significant for FPG level during phase A and for the change from baseline to final placebo phase. They also remained significant for the 2-hour OGTT during phase A and for the change from baseline to phase A.

The relation between the plasma glucose level and serum potassium concentration was studied during each phase and for the interphase changes. Table 6 shows that there was a significant inverse correlation between serum potassium concentration and FPG level in HCTZ-treated subjects during phase A and phase B and for most interphase differences. However, there

TABLE 5. *Analysis of Covariance Between Plasma Glucose Level and Other Selected Variables Demonstrating Significant Associations After Adjustment for Differences Due to the Other Variables*

Variables	Phase			Baseline			
	Baseline	A	B	Phase A	Phase B	Phase B to A	Final placebo
FPG — all hospitals							
No. of subjects	845	520	286	532	293	240	264
Hospital	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Triglycerides	<0.001	0.064	0.108	NS	NS	NS	NS
Weight	<0.001	0.001	0.069	NS	NS	0.022	NS
Drug		0.045	NS	NS	NS	0.142	0.006
Race	NS	NS	NS	NS	NS	NS	NS
2-hour OGTT — 2 hospitals							
No. of subjects	210	152	79	150	79	73	
Hospital	<0.001	<0.001	<0.001	0.060	NS	0.005	
Triglycerides	NS	0.012	NS	0.099	NS	0.120	
Weight	0.061	NS	NS	NS	NS	NS	
Drug		0.004	NS	0.007	NS	NS	
Race	NS	NS	0.087	NS	NS	0.065	

FPG = fasting plasma glucose; NS = not significant; OGTT = oral glucose tolerance test.

TABLE 6. *Correlations Between Fasting Plasma Glucose Level and Serum Potassium Concentration*

Variable	Hydrochlorothiazide			Propranolol		
	No. of subjects	r	p	No. of subjects	r	p
Baseline	342	-0.056	NS	337	0.018	NS
Phase A	275	-0.147	0.015	258	0.092	NS
Δ baseline	274	-0.281	0.000	256	0.007	NS
Phase B	173	-0.180	0.017	120	0.151	NS
Δ baseline	172	-0.210	0.006	119	0.031	NS
Δ from phase A	151	-0.167	0.041	102	-0.001	NS
Final placebo	154	0.148	NS	109	0.131	NS
Δ baseline	154	-0.024	NS	108	-0.026	NS

NS = not significant.

was no significant correlation at baseline, at final placebo phase, nor for the final placebo phase-baseline difference. In contrast, PROP-treated subjects showed no significant correlations at any time.

Other analyses were made comparing subgroups stratified according to age and initial FPG level. There were no consistent significant associations demonstrated between these characteristics and the hyperglycemic effect of the drugs.

Discussion

The evaluation of the results of the present study must take into account the facts that only men were studied, none of whom were diabetics characterized as prediabetic onset or unstable or requiring insulin for control. The changes observed might have been different in other populations of hypertensive subjects not selected according to these criteria.

The results indicate that both PROP and HCTZ increase FPG level and impair glucose tolerance irrespective of age, initial FPG level, race, and change in body weight. With respect to FPG level, the main difference between the two drugs was that the increase persisted in PROP-treated subjects 4 weeks after the dosage had begun to be tapered and 2 weeks after complete discontinuation of the drug, whereas it returned to baseline after a similar period in HCTZ-treated subjects. No other major differences in the magnitude of the increase nor in the percentage of subjects affected were noted between the drugs.

With respect to the 2-hour OGTT, the main difference between the two drugs was that the increase was significantly higher within 10 weeks in HCTZ-treated subjects. After 1 year of treatment, PROP-treated subjects also exhibited a significant increase from baseline and there was no significant difference between drugs.

A significantly greater percentage of subjects receiving HCTZ, as compared to those receiving PROP, crossed 2-hour OGTT diabetes diagnostic standards within 10 weeks. After a year of treatment, the HCTZ-treated group still exhibited a higher percentage of affected subjects, although the difference between the drugs was not significant.

The biochemical basis for the hyperglycemic effect of thiazides is not well understood, but a relation with serum potassium concentration has long been postulated.¹³ The results of the present study reaffirm this association. The findings are in harmony with those of studies using the glucose-clamp technique, which have demonstrated that under short-term experimental conditions, a decrease in serum potassium concentration is associated with impaired insulin secretion and glucose intolerance,¹⁴ while no decrease in glucose tolerance occurs under thiazide administration if the serum potassium concentration is not allowed to change.¹⁵ These data support the concept that the hyperglycemic effect of a given thiazide diuretic runs *pari passu* with its hypokalemic effect.

Both hypoglycemia and hyperglycemia have been reported with the use of β -blockers. Although of considerable clinical importance, hypoglycemia is uncommon and has been reported in conditions already predisposing to hypoglycemia, such as starvation, after exercise, after gastrectomy, after alcohol intake, after the administration of insulin or oral hypoglycemic agents in small doses, and in possible association with hypothyroidism.¹⁶⁻²⁰ It has been attributed to blockade of glucogenic and glycogenolytic mechanisms normally responsive to hypoglycemia, as well as to a possible increase in the peripheral use of glucose. Of practical importance is that catecholamine blockade can mask the sympathomimetic manifestations of hypoglycemia and thereby impede its clinical recognition. α_1 -Adrenergic stimulation, unopposed by β_2 -adrenergic counteraction, can lead to intense arterial constriction with precipitous elevation of blood pressure. The seriousness of these effects has led to the establishment of well-defined precautions in the administration of β -blockers to such susceptible persons.

Most reports of hyperglycemia associated with β -blockers have identified PROP as the culprit, but it also has been reported with other β -blockers including pindolol, alprenolol, and oxprenolol.²¹ In addition, PROP has been shown to inhibit the insulin response caused by isoproterenol²² and to depress the tolbutamide-induced insulin response.²³ Nevertheless, several investigators have noted no significant change in insulin levels in PROP-treated patients.^{24, 25} Many other factors besides insulin release can be potentially affected by β -blockade in the complex interplay of gluconeogenesis, liver and muscle glycogenolysis, and peripheral glucose utilization that controls glucose homeostasis.^{26, 27}

Both hypoglycemia and hyperglycemia have been reported less frequently with the cardioselective than with the nonselective blockers.^{25, 27, 28} This finding

would be expected since β_2 -adrenergic receptors rather than β_1 -adrenergic receptors are predominantly involved in carbohydrate metabolism. However, there is some question whether these differences are sharply defined in the therapeutic dosage range for hypertension.²⁷ This observation is consistent with the concept that there is a differential quality in the distribution of receptors and that cardioselectivity is a relative rather than an absolute property. It is also possible that the observed differences may be predicated on factors other than cardioselectivity.²⁹

The persistence of an elevated FPG level for 1 month after discontinuation of PROP in contrast with the simultaneous return to baseline in HCTZ-treated subjects is not explainable in this study by detectable differences between the two treatment populations. It is of interest that this response is opposite to the blood pressure lowering effect; in part II of this series we reported that the blood pressure rose more and faster with PROP than with HCTZ after treatment was discontinued.¹¹ The finding suggests some degree of resetting of glucose homeostasis as a result of long-term β -blocker administration. One implication is that the hyperglycemia associated with PROP may be more important in terms of long-term repercussions than that induced by HCTZ, but it is clear that this determination requires longer term observations than those performed in the present study.

The plasma glucose level changes here reported are greater and appeared earlier than in other, similar studies. In a series of 34 patients treated with thiazides, there were no significant changes in glucose tolerance during the first year of therapy; a significant deterioration was seen only 6 years later.³⁰ However, the average daily dose of HCTZ received by 13 subjects in the study was only 73 mg compared with the 93 mg received by our subjects. In another trial of 99 hypertensive men who completed 6 years of treatment after randomization to either PROP or bendroflumethiazide, there was no effect on FPG level nor on glucose tolerance.³¹ However, the maximum daily dose was 320 mg for PROP and 5 mg for bendroflumethiazide, which is considerably less than the maximum 640 mg for PROP and 200 mg for HCTZ used in the present study. In light of the relationship between dosage and hyperglycemia demonstrated in our subjects, the difference in findings is best explained by the difference in dosage. An interesting question for further exploration is whether the separate hyperglycemic effects of these drugs may be additive even in low dosage under the circumstances of long-term administration.

It seems quite definite that hyperglycemia and glucose intolerance appear earlier with HCTZ than with PROP, but that the latter also has a similar effect in time. For this reason, and in consideration of the long-term requirement of antihypertensive treatment, it appears reasonable to consider both drugs mildly diabetogenic for the purposes of antihypertensive therapy. However, it seems most doubtful in light of available evidence that this mild degree of hyperglycemia will

have any significant bearing on the vasculopathy of hypertension,⁸ although it might well be of consequence in the management of an individual patient. Whether the persistence of the PROP-induced hyperglycemic effect after discontinuing long-term administration is clinically important deserves additional investigation.

These findings do not support a preference for either HCTZ or PROP for the treatment of hypertension on the basis of their diabetogenic tendency. They do suggest that both of these drugs should be administered at their lowest effective dose and then combined if necessary with other agents to obtain appropriate antihypertensive effectiveness.

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